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PRINCIPAL INVESTIGATOR: Nicole Urban, Sc.D.

CONTRACTING ORGANIZATION: Fred Hutchinson Cancer Research Center
Seattle, Washington 98104 – 2092

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Nicole Urban, ScD

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During the fourth year of this project, the model's functionality was extended to include the simulation of populations of individuals from multiple birth cohorts. Integration of the model with a graphical Basic User Interface (BUI) was completed and more functionality was added to the model. Preliminary results were also produced, portions of model were validated, and the model was presented to four groups of scientists.

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August 22, 1997 – August 21, 1998
Year 04

Development of a Stochastic Model of the Cost-Effectiveness of Promoting Breast Cancer Screening

Nicole Urban, ScD
Principal Investigator

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ANNUAL REPORT
August 22, 1997 – August 21, 1998

INTRODUCTION

The cost-effectiveness (C/E) of screening for breast cancer remains a matter of debate despite a large number of studies addressing the issue. Most studies assess the C/E of screening strategies which have been tested in randomized controlled trials (RCTs), because effectiveness estimates are available for these strategies. As a result, little is known about the potential C/E of alternative strategies which have not been tested in trials. Similarly, little is known about the C/E of screening pre-menopausal women using different strategies or about promoting the use of screening in post-menopausal women.

The purpose of the research project is to identify efficient strategies for reducing breast cancer mortality through breast cancer screening. To identify such strategies, the trade-off between the frequency of screening among participants and the promotion of participation among underusers is being investigated. Ways to improve the effectiveness of screening in women aged 40-49 is also being explored, using new biomarkers and detection modalities, and the relative cost-effectiveness of various interventions to promote the use of regular breast cancer screening among women aged 50-80 are being evaluated. A comprehensive stochastic simulation model of the effectiveness and cost-effectiveness of breast cancer screening has been developed, and its key parameters estimated. Using the model, a variety of screening strategies can be evauated in terms of their effects on various outcomes including years of life saved and costs. Efficient strategies can be identified and their relative cost-effectiveness reported.

An annual rather than a final report is being submitted at this time because model validation efforts are ongoing. An application for a one-year no-cost extension has been submitted for this four-year project, which was funded in August 1994. A copy of the letter requesting the extension is included as Appendix A. The body of the report should be considered preliminary.

BODY

Background. There were 180,000 new cases of breast cancer, and 46,000 breast cancer deaths, in the US in 1992.[1] Screening by mammography has been shown in randomized trials as well as observational studies to be efficacious among women aged 50 to 75 in reducing breast cancer mortality.[2] Estimates of the cost-effectiveness of screening by mammography for breast cancer in women over the age of 50 range from $5,400 to nearly $140,000 per year of life saved in 1991 dollars, depending on the screening strategy evaluated and assumptions employed.[3]

A review of reports of the effectiveness of mammography screening has been completed. Randomized trials of the effectiveness of mammography screening have been conducted in the US,[4] Sweden,[5,6,7] and the United Kingdom.[8] A large demonstration project was conducted in the US,[9,10] and case-control studies have been performed in the Netherlands[11,12,13] and in Italy.[14] Evidence from the randomized controlled trials and other studies of BCS confirms that screening

by mammography every one to three years reduces breast cancer mortality among women over the age of 50.[3]

Particularly compelling is the evidence from a controlled community trial of screening by mammography conducted in Sweden in the 1970's.[5] In 19 communities allocated to the study arm, approximately 78,000 women aged 40 to 74 were offered screening by single-view mammography alone. The screening interval varied among women, but averaged about two years among the women aged 40 to 49, and 33 months among the women aged 50 to 74. Compliance was very high, 89% at the first screen and 83% at the second. At an average of six years of follow-up, overall mortality reduction was 31%, and among the women aged 50 to 74, a mortality reduction of 40% was achieved in the study communities relative to 19 control communities.

Reports of the cost-effectiveness of mammography screening have also been reviewed. Several studies have reported estimates of the cost-effectiveness of various BCS strategies including mammography.[15,16,17,18] These studies, which employ various modeling approaches, report estimates of, or assumptions about, key parameters of the problem, and provide estimates of the cost-effectiveness of mammography screening. The results of these studies are summarized below and discussed in greater detail in a review article.[3] The review was limited to studies with comparable methods addressing the cost-effectiveness of screening by mammography. Studies were included only if 1) costs per year of life saved were reported; 2) costs were defined to include screening costs, the costs associated with the diagnostic work-up of false positives, and the savings in treatment costs; and 3) both costs and benefits occurring in the future were discounted to reflect societal time preference. In the four studies which met these criteria, a discount rate of 5% was employed, in accordance with recommendations made by Russell[19] for consistency in the base-case analysis. In the review and the summary below, estimates of cost-effectiveness were adjusted for inflation using the Medical Care Price Index and reported in 1991 dollars for comparability.

The earliest study was done in 1987 by the US Office of Technology Assessment to evaluate the cost-effectiveness of BCS, defined as annual mammography in combination with CBE, in the Medicare population.[15] It was estimated that the cost per year of life saved of BCS including mammography is about $57,300, for women aged 65 to 74. The estimate was calculated over the 33-year period 1988-2020, based on the assumptions that 30% of women offered screening would accept, and that among those accepting, screening would reduce mortality by 50% at five years, gradually falling to 30% mortality reduction at 20 years. A diagnostic work-up for a false positive was assumed to be required in 2% of the women screened.

Estimates of the cost-effectiveness of mammography used alone come from studies conducted in the UK and the Netherlands. The Forrest working group produced a report in 1986 which recommended that women in the UK aged 50 to 65 be offered single-view screening mammography once every three years, a total of six screens per woman.[8] In 1988, Knox published an evaluation of that recommendation with respect to its cost-effectiveness, taking into account savings in treatment costs attributable to avoidance of mortality.[16] Knox employed a stochastic simulation model in which he assumed that the disease progresses faster among younger women than among older women. He assumed that the total average disease duration is about 5.4 years at age 25, about 7 years at age 55, and about 8.6 years at age 85. Based on the

results of the Swedish study, he further assumed that mammography detects 70% of presymptomatic disease. Compliance was set at 60%, 50%, and 40% for women aged 40, 60, and 80 respectively. His model permitted assessment of alternative screening strategies as well as the one recommended by the Forrest working group. He estimated that the cost per year of life saved of the recommended strategy was about $6,200. Although increased expenditure yielded diminishing returns in years of life saved, he reported that at least twice as much could be invested before efficiency was seriously reduced.

In the US, screening is generally performed annually or biennially rather than every three years. The cost-effectiveness of a screening program in which biennial (single-view) mammography is used alone among women aged 50 to 70 has been assessed by van der Maas and his colleagues, based on results of the Swedish and Dutch trials.[17] Like Knox, they employed a stochastic simulation model, and assumed that the mean duration of the presymptomatic phase of the disease increases from below two years among women under age 45 to more than four years among women over age 65. They assumed that screening would detect 70% of early stage disease, and based their estimate of improved prognosis attributable to earlier detection on the 29% mortality reduction in the early reports of the Swedish two-county trial.[6] The compliance rate was assumed to decrease with age from 75% at age 50 to 65% at age 70. The cost of a screen was assumed to be about $40, and about one false positive was expected for each cancer detected. Analysis of screening over the 28-year period 1988-2015 yielded a cost-effectiveness estimate of about $5,400, for biennial screening by mammography alone.

Because most women in the US receive regular CBE,[20] the cost-effectiveness of mammography when it is added to CBE is particularly relevant. Unfortunately, the results of the only effectiveness trial which has addressed this question suggest that the marginal contribution of mammography may be small.[21] However, Eddy has reported the cost-effectiveness of annual mammography relative to a baseline of annual CBE, based on the assumption that one-third to one-half the benefit of screening by the combined modalities is attributable to the mammography rather than to CBE.[18] Assuming that mammography alone costs $75, while CBE alone costs $25, Eddy estimated that the cost per year of life saved attributable to mammography relative to a baseline of CBE alone for women aged 55 to 65 was between $36,000 and $138,700, depending on assumptions about the effectiveness of screening.

The cost-effectiveness of screening for breast cancer using mammography remains a subject of debate, because previously reported estimates of the cost-effectiveness of screening by mammography vary a great deal. This variation is probably attributable primarily to differences in key assumptions such as the effectiveness of screening, the rate of false negatives and false positives, the costs of screening and diagnosis, and the potential savings in treatment costs attributable to early diagnosis. Without a simulation model it is difficult to estimate cost-effectiveness based on assumptions that seem reasonable today.

We have developed a stochastic simulation model of BCS because the software to estimate the simulation models described in the literature is either not available or inadequate, and estimates reported in the literature are based on old data. For example, the US studies[15,18] are based on assumptions about savings in treatment costs attributable to early detection which may be

optimistic. The only software readily available is CAN*TROL,[22] which is based on aggregate data and does not incorporate disease progression considerations. The stochastic simulation models employed by investigators in the UK.[16] and the Netherlands,[17] such as MISCAN[17,23]are more appropriate for identifying novel, efficient screening strategies.

MISCAN is based on a description of the disease process as a discrete, time-varying Markov chain.[23] At any point in time a patient may be in one of several states, depending on disease status. Movement between the states is controlled by transition probabilities. This representation was extensively developed by Eddy [24,25]whose states consist of an asymptomatic state, two states for cancer deaths and other deaths, and a number of prognostic states entered upon diagnosis. The transition probability from the asymptomatic state to any prognostic state is a complex function of factors which include the detection capabilities of the screening modality, a woman's screening history, and the earliness of detection. A woman who is in one of the prognostic states may only move to one of the death states; transition probabilities here are functions of age- and sex- specific mortality rates and of mortality rates from the disease which are different for each prognostic state.

In MISCAN,[23] the user is given the freedom to define a categorization of disease progression. As a result, he is responsible for specifying the distribution of sojourn time within states and transition probabilities to other states. In principal, this provides for a great deal of flexibility in the structure of the model. Thus, for example, the user may choose to simply divide the disease process into preclinical and clinical states following Walter and Day,[26,27] and to use the parameters estimated by Walter and Day[26] to specify sojourn time in the preclinical state. Alternatively, the disease process may be divided into clinical stages as in Schwartz,[28,29] with biologically-based models providing estimates of stage duration. MISCAN appears to be an appropriate tool, but it has been used to assess screening strategies which are not typical of medical practice in the US[18] Unfortunately, the software to use MISCAN is not available to US investigators.[23] Accordingly, we have built on the extensive work described above by developing a computer program to estimate a model that is consistent with data now available.

Methods. In this section of the report we describe the model which we have developed. It is a stochastic simulation model of screening for breast cancer using clincal breast examination (CBE) and mammography at varying intervals and in women with varying characteristics, including age and breast density. The approach is similar to previous models of breast cancer screening, including those of Schwartz, Eddy and Habbema, in the sense that the natural history of the disease is simulated, and the effect of screening on health outcomes and costs is modeled. The model is different from previous models in several ways. First, the natural history model takes DCIS explicitly into account. Second, the detection model accounts for the presence of calcifcations and breast density. Third, the survival model is empirically based on data from the SEER cancer registry. Fourth, costs are modeled and discounted within the simulation model. Fifth, effects of promotion on compliance with screening recommendations are modeled.

Like MISCAN, our model incorporates both disease progression characteristics and costs. It builds on previous models, including our own ovarian cancer screening model,[30] combining elements from each one. It commits to a disease process description, but allows flexibility in

defining a variety of promotion strategies and costs in addition to a range of screening options. By collaborating closely with scientists at the Applied Research Branch of the NCI, we will make our software accessible to other researchers in the US who need a more flexible and comprehensive program than CAN*TROL.

Conceptual framework. The purpose of cost-effectiveness analysis is to judge the relative efficiency of various ways to achieve a benefit, in order to guide resource allocation. Strategies to reduce disease incidence, mortality, and morbidity can be compared when analyses use the same measure of cost-effectiveness, and comparable methods. The measure most frequently recommended is the cost per year of life saved, adjusted for quality of life.[19,31] Because measurement of quality of life is costly, we use the simpler cost per year of life saved. This simplification is not expected to bias the results.[32] Consistent methods for analyzing and reporting the cost-effectiveness of prevention interventions, which have been recently recommended by Gold et al,[33] are employed. These include a societal perspective, and use of a discount rate of 3% for the base-case analysis.

A new strategy is said to be "cost-effective" if it yields an additional benefit worth the additional cost, over a defined period and relative to a defined baseline. The additional benefit (effectiveness) is measured as the change in expected years of life over the period of the analysis that can be attributed to the strategy relative to the baseline. It is calculated from age-specific rates of disease mortality and life expectancies,[34] and estimates of the relative risk of mortality associated with the strategy, usually estimated by a randomized controlled trial or a case-control study. The additional cost is measured as the change in expected costs over the period of the analysis, including the direct costs of the strategy, the costs attributable to any side effects of the strategy, and the savings in treatment costs attributable to prevention of morbidity attributable to the strategy. Both benefits and costs are specified as a stream over the period of the analysis, and discounted to the year in which the investment decision is made. The ratio of the attributable cost to the attributable benefit measures the marginal cost per additional unit of benefit of the new strategy.

In the case of cancer screening, cost-effectiveness is expressed as a ratio which measures the cost per year of life saved attributable to screening. The numerator of the ratio (net money cost) is the cost of the screening, plus the cost of diagnostic work-up for the false positives, less the savings in treatment costs attributable to earlier diagnosis among some proportion of the incident cases. The denominator of the ratio (effectiveness) is the years of life saved attributable to earlier diagnosis among the same proportion of the cases, net of any loss in life years attributable to surgical risks associated with definitively diagnosing women who screen positive, most of whom will be without cancer. This relationship can be summarized in an equation which can be expressed equivalently for a population in the aggregate, or per participant in screening.

The cost effectiveness of screening is described by the following equation:

$$C/E = (c_{scr} + c_{dx} + c_{tr})/pyls \qquad (1)$$

where:

c_{scr} = cost of screening including mammography,

c_{dx} = expected cost of diagnosis attributable to mammography screening,

c_{tr} = expected cost of treatment attributable to mammography screening, and

pyls = potential years of life saved attributable to mammography screening.

In general, c_{tr} is assumed to be negative due to a presumed savings in treatment costs associated with earlier diagnosis of breast cancer[15] although empirical evidence for such a savings is sparse.[35] If savings in treatment costs are sufficient to offset the costs of screening and diagnosis, then BCS is said to be cost-saving.[36] Otherwise, a cost-effectiveness ratio is calculated which measures the cost per additional year of life that can be saved through BCS.

Assessment of the cost-effectiveness of promoting screening by mammography ($[C/E]_{prom}$) requires an additional term in the equation, and an additional step in the analysis. The additional step is evaluation of the impact on participation in mammography screening of the promotion effort relative to its cost, which yields an estimate of the cost per additional participant in screening, denoted by C_{prom} in the equation below. The baseline for the analysis is participation in screening in the absence of the promotion program. Evaluation of the impact on health and costs of participation in mammography screening, which yields the cost per year of life saved of screening by mammography, is still required for the analysis. Each additional participant can be assumed to incur the same costs, and experience the same benefits, as women who would participate in mammography screening in the absence of the promotion intervention. Alternatively, it can be assumed that the costs and benefits are different for the additional participants, due to self-selection bias. Sensitivity analysis can be used to accommodate the need to consider alternative assumptions.

Model design. A stochastic simulation model has been developed, building on our experience with modeling ovarian cancer screening as well as on the work of others. The core of the model is biological,[28] incorporating assumptions about growth rate and metastatic spread of the disease from the time of inception. Clinical detection is a function of disease progression. The age of onset of preclinical disease is generated by backcalculation from age-specific incidence curves, generating a preclinical sojourn time distribution which is consistent with that reported by Walter and Day.[26,27] The properties of the BCS modalities (sensitivity, specificity), are obtained from the literature on methods for BCS. These properties depend on the state of disease progression at the time of diagnosis as well as on the woman's screening history. Assumptions about the effectiveness of the interventions to promote BCS, as well as information from previous screening trials about the frequency of screen refusal, are used to determine whether a woman attends a screen. Survival from date of diagnosis is a function of several factors, the most important of which is the disease status at diagnosis. The survival models used are based on survival by clinical stage, estimated from SEER data. Because several authors[37,38] have suggested that tumor growth rate may play an independent prognostic role, we model this phenomenon and examine whether it increases the agreement between our model-generated survival times and observed survival times.

Like CAN*TROL and MISCAN, the model also incorporates costs. After the woman's characteristics (age at onset, disease progression date) are generated, she is entered into a screening protocol defined by the user. For example, she might receive annual screening by CBE and mammography, or she might receive an annual CBE followed by mammography and ultrasound only if a tumor was suspected clinically. Costs of the application of the screen(s) are added to the numerator of the cost-effectiveness ratio. Results of the CBE and mammography are a function of the woman's disease status at the time of the test, but include a randomly generated error component consistent with assumptions provided by the user about the sensitivity and specificity (rates of false positivity and false negativity) of the tests. For true positives, if the screen-detected cancer results in diagnosis at an earlier stage, the years of life saved attributable to earlier detection are added to the denominator of the cost-effectiveness ratio, and the savings in treatment costs subtracted from the numerator of the cost-effectiveness ratio. For false positives, the costs incurred of making the definitive diagnosis are added to the numerator of the cost-effectiveness ratio. For false negatives, no costs or benefits are accrued; the disease continues to progress until it is detected clinically or the next screen has an opportunity to detect it. Discounting is performed by the program and net present values are reported. The simulation is repeated to assess the cost-effectiveness of each alternative screening strategy. For each strategy, the user specifies the age at which women are to start screening and the screening interval for the application of each detection modality.

Sensitivity Analyses: Base-case assumptions for estimating cost-effectiveness must be made despite conflicting evidence in the literature regarding their values. Sensitivity analysis is used to estimate cost-effectiveness using "worst-case" or "best-case" assumptions, in order to get a sense of the range of cost-effectiveness estimates. Sensitivity analysis is being used extensively to vary assumptions about 1) the discount rate (3% for the base-case), 2) the period of the analysis (30 years for the base-case), 3) efficacy of screening (30% mortality reduction in the base-case), and 4) the costs of promotion, screening, diagnosis, and treatment.

Simulation methods. The model is programmed in Gauss, an interpreted matrix manipulation language, and run on a dual processor Pentium II computer. 10-20 minutes are required to complete a simulation run of 1 million women, depending on the complexity of the simulation. The Gauss model may be controlled through a graphical Basic User Interface (BUI), implemented in FoxPro, that allows modification of all parameters without programming the Gauss model itself. The BUI also formats model output for viewing and stores parameter sets and output from previous runs.

As a stochastic microsimulation model, the model uses streams of pseudo-random numbers to choose characteristics for individuals. The streams of random numbers may be controlled to exactly replicate runs. Such "equal-luck" runs are used in sensitivity testing to vary individual parameters one at a time and observe their effects on outputs while holding all other factors, including chance, constant.

Data. The primary source of data for model parameters is the Surveillance, Epidemiology and End Results (SEER) database. SEER data provided distributions for incidence and survival dependent on age, stage, tumor size, and calendar year. Size and stage data from SEER were used to determine distributions of size at metastasis.

As clinical detection is the baseline against which screening is assessed, the SEER population from 1973 to 1982 is taken to represent a population in the absence of mass screening by mammography. 1973 is the earliest year of the SEER records and 1982 is the last year in which screening mammography was insignificant in the United States.

Additional parameters were drawn from a wide range of sources in the scientific literature. These are cited as they occur in "Model Structure," below.

Model structure - Natural History of Disease. The model begins at the point of clinical detection and simulates tumor development backward in time to the point of earliest inception. Age, stage, and size at clinical detection are randomly assigned from distributions drawn from the SEER population. Once an individual has been given these initial cancer characteristics, or the determination has been made that the individual never contracts breast cancer in her lifetime, the progress of the disease is traced backwards.

The model contains an explicit biological model of cancer development in which tumor volume is assumed to increase at a constant rate. Estimates of the rate of progression of breast cancer are presented in Table 1.[39,40,41,42,43,44] The rate varies from individual to individual and with age, with tumors growing faster on average in younger women.[45] Tumors are assumed to be spherical for ease of calculation, but the assumed shape of the tumor does not affect model results if the tumor proportions remain constant as it develops.

Since the model works backwards in time, tumors shrink from size at clinical detection down to a minimum size that defines the boundary between invasive tumors and in situ disease. This minimum size has been set to 0.2 cm. It is not a biological parameter so much as a definition of the size of an invasive area of an in situ lesion that a pathologist would be likely to detect and use to classify a lesion as invasive rather than in situ.

The in situ phase itself is given a duration only; no size is assigned. Lobular carcinoma in situ is not modeled as it appears to be a risk factor rather than a true precursor of invasive cancer, and in any case cannot be reliably detected by mammography. Ductal carcinoma in situ, DCIS, is modeled as a precursor of all invasive ductal breast cancer. DCIS appears to invade at a constant rate;[46] an exponential distribution of duration is therefore used.

The shape of the exponential distribution dictates that some durations will be very short, so short that the DCIS stage is unlikely to be detected by screening. Some invasive lesions will therefore appear not to pass through a DCIS stage. Other DCIS durations will be very long, necessitating a limit. The youngest age at which an individual is allowed to contract DCIS is set to 25 in the model.

The same distribution is used to set the duration of DCIS detected clinically. Although a rare disease, it did account for 5% of breast cancer before the advent of screening mammography.

Disease that is metastatic at clinical detection is given a size at metastasis using an odds ratio technique.[47] Using the proportion of metastatic tumors at given sizes in the SEER population, a curve showing probability of metastasis by a given size is generated. From the probability curve,

a size at metastasis less than size at diagnosis is generated for each individual with metastatic disease. Metastasis is defined as either metastasis to nodes or distant metastasis (SEER Historic Stage Regional or Distant).

Model structure - Screen Detection. The detection component of the model as it relates to the natural history of the disease is depicted in Figure 1. The disease characteristics of interest are the likelihood of detection by screen tests and the effect of the disease on survival. Broadly, detection is thought to become less likely earlier in the lesion's natural history, while survival is thought to improve the earlier the lesion is detected.

Detection by mammography is modeled in two components, corresponding to detection of the tumor mass and detection by all other signs (microcalcifications etc). Each tumor is assigned a size at earliest detectability: any mammogram given after the tumor reaches that size will automatically detect the tumor. Below that size, and for all DCIS, a lesion is given a probability of detection that varies by breast density at the time of the test. Test results prior to reaching size at detectability are independent except for the (small) effects of breast density; test results once a tumor is detectable size are highly dependent.

Model structure – Survival. Survival after detection of breast cancer is modeled as two separate cause-specific survival times. Breast cancer survival is determined conditional on the age, stage, and size at diagnosis, as well as the calendar year of diagnosis for population simulations. Non-cancer survival is conditional on age at diagnosis and calendar year of birth. These two times are generated independently from relative survival curves and the earlier chosen as the observed time of death. Cause of death is also determined as the earlier cause.

Survival is generated twice, once for breast cancer in the absence of screening and again with screening. Age at death from causes other than cancer remains the same in either case, as does age at death from cancer if detection was not advanced by screening. With early detection, there is the potential for savings of years of life.

Breast cancer survival with and without screen detection is generated at the same percentile from the survival curves, limiting the degree to which survival can change with screen detection. This practice, along with accounting for lead time by adding it to survival time, largely eliminates the possibility of worse survival with earlier detection. Simulation runs do not, in general, produce many individuals who lose years of life due to early detection by screening. In the few cases where this does occur, it can be attributed to changes in survival with calendar year. For some breast cancer stages, survival has improved over the years (SEER) (possibly due to improvements in treatment), so that earlier detection can lead to worse survival.

Model structure – Costs. Each screen test is assigned a cost, and false positive test results are assigned additional costs.[48,49] These are discounted and summed to produce total costs of screening. Treatment costs are assigned by stage at diagnosis and by phase of treatment.[50,51] The phases include the costs of initial treatment in the first six months, maintenance costs, and terminal costs for the last six months of life. Short-term survival, less than 18 months, is accounted for in a separate category. These costs are also discounted and summed to produce total costs of

treatment. By recalculating these costs with and without screening, a net cost of screening may be derived equal to test costs plus treatment with screen minus treatment without screen.

Model structure – Promotion. If mass screening with mammography is cost-effective, the question of how best to promote it becomes of interest. Promotion also entails costs, so that the cost-effectiveness of promotion, as well as the screening strategy promoted, can be evaluated.

Using the results of the Breast Cancer Screening Consortium studies, which are expected to be available in 1999, to provide parameters for costs of promotion and results in terms of increases in mammography usage, the model calculates the expected years of life saved due to screening additional women and the total costs of screening them, including costs of promotion, screen tests, and net treatment costs. The costs of promotion observed in one of these studies--$500 per additional user in one study arm—are converted to a cost per test in the population, added to test costs, discounted and summed along with the costs of mammograms.

Preliminary results. Reports have not been prepared because validation has not been completed. However, the model generates estimates which have face validity in the sense that they are consistent with expectations based on previous reports on the literature. Selected model outputs are reported in Figures 2. and 3. for biennial and annual mammography respectively, among women aged 50-80.

Preliminary estimates of the effects of promotion and screening younger women have also been made using the model. Dr. Urban and Mr. Gable participated in the November, 1997 "DOD Breast Cancer Research Program: An Era of Hope" conference. A poster was presented showing results to date on the cost-effectiveness of mammography over a range of ages and promotion of mammography among women age 50-80. When age at first screen was reduced from 50 to 40, the cost per year of life saved attributable to mammography rose 38% from $21,000 to $29,000. Total years of life saved rose 15% from 8.0 months per cancer case to 9.2 months per case. Promotion resulted in a 7% increase in YLS, but costs of promotion varied greatly depending on the need to repeat the promotional activity to maintain its effect. Costs rose 7% with a one-time promotion, 57% when repeated promotions were necessary. These results, depicted in Figure 4, are preliminary estimates and should be interpreted with caution.

A paper describing model methods and presenting findings on ductal carcinoma in situ (DCIS) is in preparation. As the biology of DCIS is relatively little understood, in other simulation studies of mammography it has been given cursory treatment or omitted. The incidence of DCIS has increased threefold in the US since widespread adoption of mammography in the early 1980's, from 4% of all breast cancer cases to 12%, contributing about half the observed rise in absolute incidence. Under the range of assumptions used in our model, mammography causes a 50% - 400% rise in incidence of DCIS, with the most likely estimate at 200%. Early detection of DCIS accounted for as much as 40% of all years of life saved due to mammography. Screen-detection of DCIS resulted in the prevention of clinical invasive disease approximately 1 out of 3 times, with the remainder merely advancing diagnosis of clinical DCIS or finding lesions that otherwise would not have become apparent during the woman's lifetime. 1 in 10 screen-detected DCIS resulted in savings of years of life, compared to 1 in 4 screen-detected invasive cancers.

The estimates reported above should be considered preliminary because validation has not been completed. This is important because preliminary results have been found to be highly sensitive to some assumptions, particularly to the length of the preclinical detectable period and the probability of screen detection at various points in tumor development. Early validation efforts suggest that the model may underestimate the mortality reduction due to screening. The key assumption made with respect to survival is that screen-detected cases will experience survival similar to that of clinically detected cases with the same stage, size, and age. Underestimates of mortality reductions suggest that screen-detected cases may experience better survival than equivalent clinically-detected cases. Note that lead time and length bias are already accounted for by the model: each tumor is assumed to have the same "deadliness" with and without screening, and that deadliness is linked to the tumor's growth rate and, hence, to the likelihood that screening mammography will detect it. The possibility remains that tumors allowed to develop until they produce symptoms are more deadly than tumors discovered before they become symptomatic. Screening will then save more years of life than is indicated by the effects of stage shifts alone.

Progress and plans for the coming year. During the fourth year of this project, the model's functionality was extended to include simulation of populations of individuals from multiple birth cohorts. Integration of the model with a graphical Basic User Interface (BUI) was completed, more functionality was added to the model, preliminary results were produced, and the model was presented to four groups of scientists.

We continued our collaboration with NCI investigators on the Population Simulation (POPSIM) project, the goal of which is to extend existing microsimulation models to allow simulation of multicohort populations. Cohort-specific parameters for cancer incidence, cancer survival, survival in the absence of cancer, and dissemination of mammography were collected and integrated into the model. The model is now able to simulate screening in a population using parameters representing the US population. Multicohort populations such as controlled trial populations may also be simulated.

Mr. Gable, Lauren Clarke, and Ray Cha, the builders of breast, ovarian, and prostate cancer models, respectively, traveled to NCI headquarters in May, 1998 to discuss the POPSIM project with collaborators, Drs. Eric Feuer and Julie Legler. At this meeting, Mr. Gable presented the breast model to a group of NCI staff scientists, describing model structure, assumptions, data sources and preliminary results. In addition, Mr. Gable presented the model to a working group on cost-effectiveness analysis at the Fred Hutchinson Cancer Research Center and spoke at a postdoctoral seminar on cost-effectiveness analysis in public health at the University of Washington, both in Seattle in November 1997.

In the no-cost-extension year, validation of the model will be completed and reports will be prepared. Validation work has been delayed by significant structural changes and introduction of new parameter sets in connection with the POPSIM effort. As the model has been in flux, validation had to be deferred until a stable set of input parameters was in place.

A new investigator from the Department of Biostatistics at the University of Washington, Dr. Martin McIntosh, joined the group in late 1997 to work with investigators to validate the model.

Dr. McIntosh has collected and analyzed data from the Health Insurance Plan of New York's randomized clinical trial of mammography (the HIP study) in preparation for using that data in validating the model, and he assisted in the development of a validation strategy.

The validation strategy is as follows. Model parameters are sorted into three groups by importance in validation: 1) setup; 2) low uncertainty or sensitivity, and 3) high uncertainty and sensitivity. The seven setup variables present in the model, shown in Figure 5, do not require validation because they merely describe the events being simulated. The ten variables of low uncertainty or sensitivity, shown in Figure 6, are demographic parameters like survival curves that are derived from large databases, or those like cost of mammograms that relate in an uncomplicated way to outputs. These first two groups can be set aside and validation efforts concentrated on the third, shown in Figure 7. There are six variables for which the uncertainty of the estimates is high and the effect on model output may also be high. We will systematically vary each and observe the effects on outcomes of interest. Those that have a significant effect on outcomes will be the focus of efforts to improve our estimates and will be included in uncertainty analyses around any final results obtained from the model.

Rob Boer, an investigator from the MISCAN modeling group in Nijmegan, the Netherlands will travel to Seattle in April and May 1999. We will compare in detail their model of the cost-effectiveness of breast cancer screening with ours. The MISCAN models utilize an abstracted stage-transition model of the natural history of breast cancer, while our model commits to an explicit biological model driven by changes in tumor size, among a number of other differences in approach. We hope to uncover assumptions in our two models that would not otherwise be readily apparent, and plan to make changes in our models if appropriate.

In addition to the paper on methods and DCIS, we plan to draft additional papers on relative cost-effectiveness of selected screening strategies and the cost-effectiveness of promotion of mammography.

CONCLUSIONS

Screening for breast cancer by mammography may be more cost-effective in women aged 40-49 than previously thought, if DCIS detected by mammography would otherwise have progressed and been diagnosed as invasive cancer. Careful validation of the model is required to strengthen this conclusion, which must be viewed as very preliminary.

Doubling Times (DT) of Breast Tumors

◆ Peer et al (1993)	24 - 640 d
◆ Kuroishi et al (1990)	11 - 1293 d
◆ Kusama et al (1972)	6 - 540 d
◆ Koscielny et al (1985)	15 - 855 d
◆ Galante (1983)	60 d
◆ Tabbane (1989)	115 d
◆ Philippe, Le Gal (1968)	40 d

Table 1

Efficacy of Screen Tests

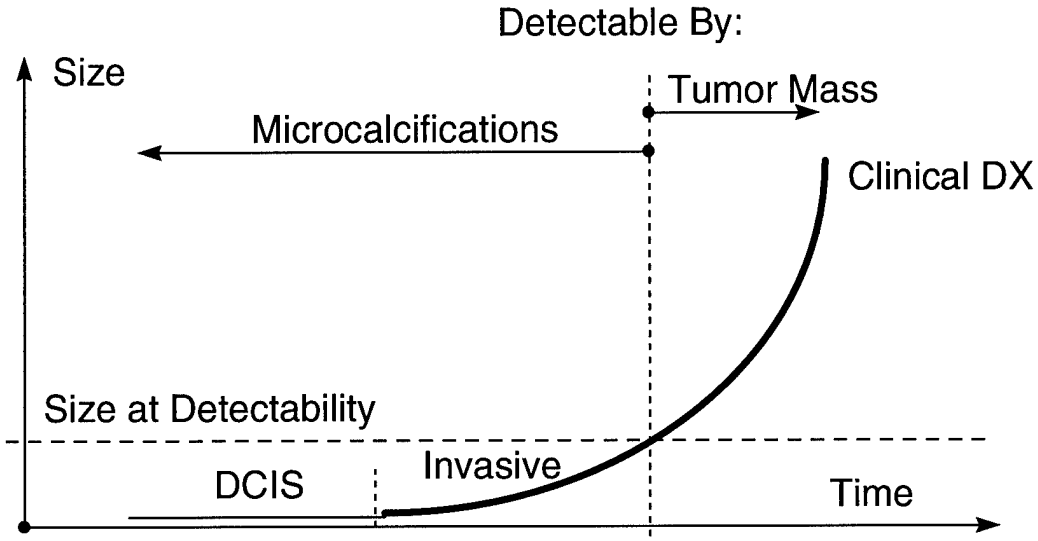

Figure 1

Sample Output: Biennial, Ages 50-80

- 0.55 YLS/Case
- $38,640 /YLS
- 16% Reduction in Cancer Mortality
- 17.3% Increase in Cancer Incidence
- 87.9% Sensitivity
- 94.8% Specificity
- 1.9 yr Mean Lead Time
- 8.5 yr Mean Sojourn Time

Figure 2

Sample Output: Annual, Ages 50-80

- 0.81 YLS/Case
- $49,267/YLS
- 24% Reduction in Cancer Mortality
- 21.4% Increase in Cancer Incidence
- 84.8% Sensitivity
- 94.7% Specificity
- 2.5 yr Mean Lead Time
- 8.5 yr Mean Sojourn Time

Figure 3

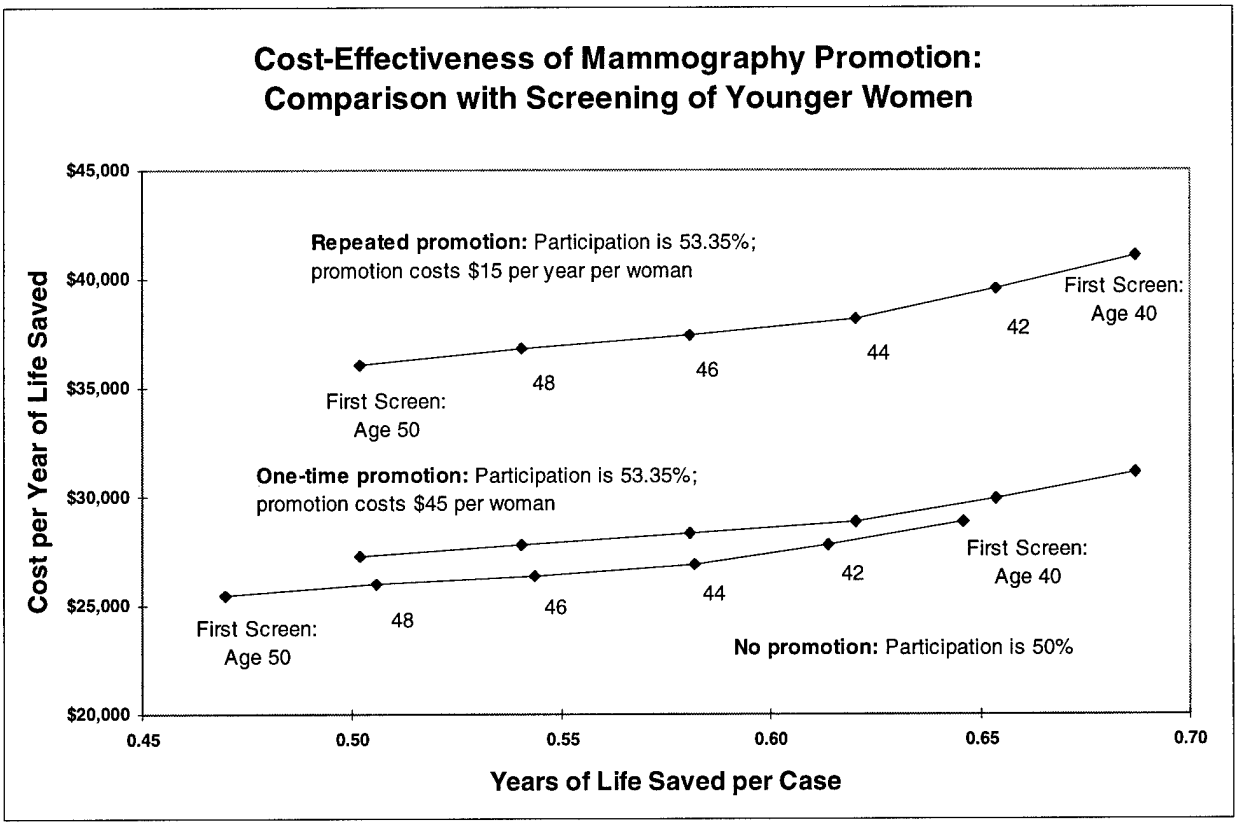
Cost-Effectiveness of Mammography Promotion:
Comparison with Screening of Younger Women
$45,000
$40,000
$35,000
$30,000
$25,000
$20,000
Cost per Year of Life Saved
Repeated promotion: Participation is 53.35%;
promotion costs $15 per year per woman
First Screen:
Age 50
48
46
44
42
First Screen:
Age 40
One-time promotion: Participation is 53.35%;
promotion costs $45 per woman
First Screen:
Age 50
48
46
44
42
First Screen:
Age 40
No promotion: Participation is 50%
0.45
0.50
0.55
0.60
0.65
0.70
Years of Life Saved per Case

Figure 4

Validation:
Setup Variables

- Number of Individuals in Population
- Youngest and Oldest Ages Simulated
- Ages at Start and End of Screening
- Screening Interval
- Proportion of Population Screened
- Length of Follow-up for False Negatives
- Discount Rate

Figure 5

Validation: Variables with Low Uncertainty or Sensitivity

- Age- and Stage-Specific Clinical Incidence
- Age- and Stage-Specific Size at Clinical Incidence
- Age-Specific Size at Metastasis
- Breast Density Distribution and Transition Probabilities
- Specificity of Mammography
- Life Tables
- Age-, Stage-, Size- and Period-Specific Survival
- Cost of a Mammogram
- Costs of False Positives
- Phase-Specific Costs of Treatment

Figure 6

Validation: Variables with High Uncertainty and Sensitivity

- Tumor Growth Model
- DCIS Stage Length Model
- Size at Invasion
- Size at Earliest Detectability
- P{Detect Small Lesion}
- P{Lesion is Never Detectable}

Figure 7

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September 18, 1998

Jean M. Shinbur
Contracting Officer
U.S. Army Medical Research Acquisition Activity
Attention: SGRD-RMA-RG
Fort Detrick
Fredrick, MD 21702-5014

Dear Ms. Shinbur:

Funding for the project entitled "Development of a Stochastic Simulation Model of the Cost-Effectiveness of Promoting Breast Cancer Screening" (contract # DAMD17-94-J-42377) is scheduled to end September 21, 1998. We would like to request an extension of this time limit.

Work to date has produced a microsimulation model which is being used to carry out the tasks described in the original proposal.

The simulation model generates:

- Individual women, their birth and death in the absence of breast cancer, cancer incidence, the natural history of each lesion, and the success or failure of screening based on each natural history.
- A calculation of survival after diagnosis of breast cancer in both the absence and presence of screening.
- A cost analysis evaluation of screening, treatment, and promotion of mammography.

A decision was made to add additional capabilities to the model beyond those originally envisioned when the opportunity to do so was presented to us by a group of scientists at the National Cancer Institute. These scientists, Drs. Eric Feuer and Julie Legler of the Applied Research Branch of NCI, wished to explore the effects of mammography on breast cancer incidence and mortality in the United States from 1980 to 2000. This question required us to extend most of the components of the model to take account of cohort effects, that is, the changes in incidence, survival and so forth that have occurred through time. Drs. Feuer and Legler offered their

assistance and the resources of the NCI in gathering the expanded model parameters. Also, as part of this work, we created a user-friendly graphical interface for the model, which formerly required programming expertise to use.

The collaboration with the NCI scientists has produced a significantly stronger and more flexible model. However, the additional work has put us behind schedule, as did a gap in staffing in Years 01 and 02. The model produces complete output now, but our confidence in the results is not yet sufficient for us to submit a final report.

We are currently in the process of validating the model, which involves comparing model output in detail against outside data sources to gauge its accuracy. This last stage of model development can provide some of the greatest benefits of the modeling exercise, and the desire to perform it well is our largest motivation for requesting additional time.

Due to the overall importance of finishing the last stage of work and refining the model, we would like to request a 12 month no cost extension until September 1999. We will provide a comprehensive report as soon as validation is completed and data are available.

Thank you for your consideration of this request. If you have any questions, please feel free to contact me at (206) 667-4677.

Sincerely,

Nicole Urban, Sc. D.

Principal Investigator